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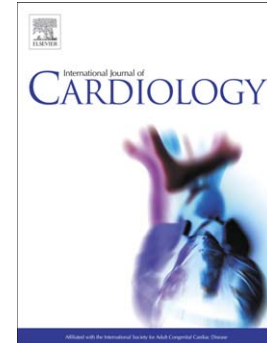
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**Non-Vitamin K Oral Anticoagulants (NOACs) for stroke prevention in Asian patients  
with atrial fibrillation: Time for a reappraisal**

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**Author contribution:**

G.Y.H. Lip made main contributions in study conception, data interpretation and

manuscript drafting/revisions. KL Wang made the primary contribution in data collection, figure drawing, and manuscript drafting/revisions. CE Chiang made the contribution to study conception, data interpretation and manuscript revisions. All authors contributed to interpretation of results, revising the manuscript critically for important intellectual content, and all approved the final manuscript.

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### Abstract

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) have changed the landscape for stroke prevention in atrial fibrillation (AF). Given the huge burden of AF in Asians, more attention to stroke prevention is clearly needed. Aiming to provide an overview and reappraisal of stroke prevention in Asians with AF, we searched MEDLINE for information on NOACs in Asians. In addition, abstracts from national and international cardiovascular meetings were studied to identify unpublished studies. In the 4 recent Phase 3 trials comparing NOACs to warfarin, a consistent pattern is evident. For efficacy endpoints in the comparison of NOACs vs warfarin, a significant reduction in stroke/systemic embolization was seen for dabigatran 150mg [HR 0.45 (0.28-0.72)], with non-significant trends seen for lower stroke/systemic embolization with other NOACs, except edoxaban 30mg. A similar pattern was seen for ischaemic stroke, with a significant reduction for dabigatran 150mg [HR 0.55 (0.32-0.950)]. For haemorrhagic stroke, all NOACs regimes, except rivaroxaban 20mg, had significantly lower hazard ratios. No evidence of increased myocardial infarction was found for NOACs. All-cause mortality was significantly lowered amongst Asian patients on edoxaban 60mg compared to warfarin [HR 0.63 (0.40-0.98)] with non-significant trends to lower mortality with dabigatran 150mg, rivaroxaban and edoxaban 30mg.

For safety endpoints, all the NOACs regimes, except rivaroxaban 20 mg, significantly reduced major bleeding and 'all bleeding' events. Intracranial haemorrhage was consistently lowered by all NOACs. None of NOACs increased gastrointestinal bleeding. These information suggested that NOACs should be preferentially indicated for stroke prevention in Asians with AF.

**Key words** anticoagulant, Asia, atrial fibrillation, stroke, thromboembolism

## Introduction

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia, and represents a global problem [1]. Whilst the prevalence is broadly similar to epidemiological data from Western countries, given the size of the increasingly elderly Asian population (for example, in China), the absolute numbers of patients with AF in Asia are substantially higher than Europe or the United States [2]. Given the AF confers a substantial risk of mortality and morbidity from stroke, thromboembolism, heart failure, cognitive impairment and poor quality of life, the public health and healthcare burden associated with AF is huge.

Stroke prevention is central to the management of AF, given the increased risk of stroke and thromboembolism associated with this arrhythmia. Strokes associated with AF are associated with a higher mortality, greater disability, longer hospital stays and lower rates of discharge to one's own home.

Whilst it is well established that effective stroke prevention requires oral anticoagulation (OAC), the problem until recently was compounded by the substantial numbers of patients in Asia that are not treated with OACs (usually



Vitamin K Antagonists (VKAs, eg. warfarin), and even those managed with VKAs have poor quality anticoagulation control (as reflected by poor time in therapeutic range (TTR)) or not having access to a structured anticoagulation monitoring service [2, 3]. High quality anticoagulation control (eg average individual TTRs >70%) has been associated with low rates of stroke and bleeding [4-6]. Thus, stroke rates whilst on warfarin therapy in some 'real world' Asian cohorts (where TTR is poor) are no different to those on aspirin or those untreated [7].

The availability of Non-VKA Oral Anticoagulants (NOACs, previously referred to as new or novel OACs [8] has changed the landscape for stroke prevention in AF. These drugs offer relative efficacy, safety and convenience compared to the VKAs. The NOACs fall into 2 categories – the oral direct thrombin inhibitors (eg. dabigatran) and the oral Factor Xa inhibitors (eg. rivaroxaban, apixaban and edoxaban) and have been compared to warfarin in large Phase 3 clinical trials. These trials were conducted as global trials, and substantial numbers of patients from Asian countries were participants.

The objective of this review is to provide an overview and reappraisal of stroke prevention in Asian patients with AF, with particular focus on the data on NOACs in

Asians.

### **Search strategy**

We searched MEDLINE using the following terms individually and/or in combination: 'Asians', 'atrial fibrillation', 'stroke', 'thromboembolism', 'anticoagulation', 'antiplatelet therapy', 'dabigatran', 'rivaroxaban', 'apixaban', 'edoxaban', 'direct thrombin inhibitors', 'Factor Xa inhibitors', 'NOACs'. In addition, abstracts from national and international cardiovascular meetings were studied to identify unpublished studies. The extensive detailed literature on the underlying pathophysiology of thromboembolism AF will not be addressed in this article, which particularly concentrates on the management aspects.

### **Epidemiology – a brief overview**

Much of the epidemiology of AF comes from Western countries. A recent systematic review of epidemiology of AF in regions outside North America and Europe found that the reported prevalence of AF varied among countries, with

different ranges in community- and hospital-based studies (0.1%-4% and 2.8%-14%, respectively) [1]. The use of anticoagulant therapy varied widely among countries and studies, as did the reported prevalence of stroke in patients with AF (2.8%-24.2%).

Specific data on associated comorbidities from surveys and cohort studies of AF from various Asian countries, compared to non-Asians are summarized in Table 1 [3, 9-15]. The average age and proportion of females in Asians and non-Asians was broadly similar. As with Western countries, the most prevalent associated comorbidity was hypertension, with a trend towards a higher proportion with prior stroke/transient ischemic attack (TIA) amongst Asian patients. Other comorbidities were broadly similar, although formal comparisons across the different studies are difficult given the differences in study design and setting.

Table 2 summarises the main comorbidities from the Asian patients included in the 4 large Phase 3 randomised trials [16-19]. In RE-LY, the prevalence of heart failure, hypertension, diabetes, and the mean CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age $\geq$ 75 [doubled], Diabetes, Stroke [doubled]) score were broadly similar between Asians and non-Asians. There was a lower proportion of those age  $\geq$ 75 in Asians, with a higher proportion with prior stroke/TIA. In ROCKET-AF, the

East Asian cohort had a lower prevalence of heart failure and hypertension, and again, had higher proportion with prior stroke/TIA. In ARISTOTLE and ENGAGE-AF, Asians had lower prevalence of heart failure and higher proportion of prior stroke/TIA. In ENGAGE-AF, the proportion with heart failure, hypertension tended to be lower, compared to non-Asians.

The burden of AF-associated stroke is probably higher in Asians, but the value of OAC is maintained. In a recent study amongst 2339 elderly (age  $\geq 80$ ) hospitalized Chinese patients from Hong Kong, elderly Asians had higher stroke rates after a 2.2-year follow-up as high as 80.8% on no antithrombotic therapy [3, 20].

Whilst the data from Hong Kong are generally reassuring, other considerations are necessary. Proportionally the ratio between ischaemic stroke to haemorrhagic stroke is lower in Asians compared to non-Asians [21]. Also, Asian patients have a higher mortality due to warfarin-induced intra-cranial haemorrhage (ICH) (62%) compared to Caucasians [22]. Nonetheless, the higher risks associated with Asians, may not be a problem solely with warfarin. In the Hong Kong series, for example, the annual incidence of ICH in patients taking aspirin and warfarin was 0.77% per year and 0.80% per year, respectively [3].

*Stroke risk assessment*

Whilst AF increases the risk of stroke five-fold, this risk is not homogeneous, and is dependent upon the presence of stroke risk factors. Stroke risk stratification has been made using risk scores such as the CHADS<sub>2</sub> score, which derived 5 common stroke risk factors from the non-VKA arms of the historical trial cohorts[23] [24]. The latter trials have been criticized for randomizing <10% of patients screened, and many risk factors were not recorded nor consistently defined. The CHADS<sub>2</sub> score was used to categorise 'high risk' patients to be targeted for VKA therapy (but numerous studies still showed that high risk patients were undertreated). Also, the predictive value of this score was modest (c-statistic approx. 0.6) and in recent Asian cohorts, the CHADS<sub>2</sub> score did not significantly predict stroke [3, 7].

More recently, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [25] (Congestive heart failure, Hypertension, Age  $\geq 75$  [doubled], Diabetes, Stroke [doubled]-Vascular disease, Age 65–74, Sex category [female]) has been recommended for stroke risk assessment, by the latest major guidelines from the European Society of Cardiology (ESC), Asia-Pacific Heart Rhythm Society (APHRS), American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) and the National Institute for

Health and Care Excellence (NICE). The CHA<sub>2</sub>DS<sub>2</sub>-VASC score is more inclusive of common stroke risk factors in AF, and performs best at initially identifying the 'low risk' AF patients (ie. CHA<sub>2</sub>DS<sub>2</sub>-VASC score =0 in males, score=1 in females) who do not need any antithrombotic therapy. Subsequent to this initial step, stroke prevention can be offered to AF patients with  $\geq 1$  additional stroke risk factors ie. CHA<sub>2</sub>DS<sub>2</sub>-VASC score = 1 (males) or  $\geq 2$  (everyone).

The CHA<sub>2</sub>DS<sub>2</sub>-VASC score has been validated in various Asian populations, including those from China, Hong Kong, Taiwan, South Korea and Japan. Indeed, CHA<sub>2</sub>DS<sub>2</sub>-VASC (but not CHADS<sub>2</sub>) was a significant predictor of stroke/systemic embolization in Asian patients with AF [3, 7, 26], thus justifying its adoption in the major guidelines.

#### *Bleeding risk assessment*

Various risk scores for predicting bleeding in AF have been proposed, but until recently, uptake has been poor due to their complexity and (in some cases) the need to quantify some parameters, such as 'genetic factors' [27].

More recently, the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke,

Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly) score has been proposed as a simple clinical score to predict clinically relevant bleeding in AF patients [28], and this score has now been well-validated to predict major bleeding and intracranial bleeding. HAS-BLED outperformed all other bleeding risk scores and has also been validated in VKA and non-VKA anticoagulated patients. Furthermore, HAS-BLED has been validated in Asian patients[7]. The HAS-BLED score has been recommended in the major guidelines from the ESC, Canadian Cardiovascular Society and NICE [29-31].

Nonetheless, the HAS-BLED score needs to be used appropriately, and a high score is not an excuse to withhold OAC but to 'flag up' patients potentially at risk for bleeding for more careful review and follow-up. Also, HAS-BLED makes the clinician think about the correctable risk factors for bleeding, such as uncontrolled hypertension (the 'H' in HAS-BLED), labile INRs (L, only applies on a VKA patient), concomitant drugs such as aspirin or NSAIDs or alcohol excess/abuse (the D in HAS-BLED). A risk of falls per se is not an independent predictor for OAC-related bleeding [32].

### **Aspirin in Asian patients**

What about antiplatelet therapy? In the historical trials, aspirin had a small and non-significant 19% reduction in stroke, with no impact on mortality [33]. This 19% reduction was driven by the one single positive trial (SPAF-1) which had major internal heterogeneity for the aspirin effect against placebo/control, reducing stroke by 94% in anticoagulation-eligible patients and by only 8% in anticoagulation-ineligible patients. The SPAF-1 trial used aspirin 325mg daily and had been stopped early hence possibly exaggerating the aspirin efficacy results. Also, aspirin did not reduce strokes in those age >75, nor did it prevent severe strokes.

The data for the efficacy and safety of aspirin in Asian patients with AF are similarly weak. In the Chinese AF cohort study from Hong Kong, the stroke rate was 66.9% in patients on warfarin compared with 80.8% in patients with no antithrombotic therapy (hazard ratio, 0.53; 95%CI 0.48-0.58;  $P<0.001$ ). Aspirin had a non-significant 18.7% reduction in ischaemic strokes. In contrast, warfarin-treated patients also had a better mortality rate (hazard ratio, 0.40; 0.37-0.45;  $P<0.0001$ ) and ischemic stroke rate (hazard ratio, 0.64; 0.54-0.77;  $P<0.0001$ ) [3, 20]. As mentioned above, the ICH rate in Chinese patients taking aspirin and warfarin was 0.77% per



year and 0.80% per year, respectively [3]. Analysis of the net clinical benefit favored the use of warfarin over aspirin or no therapy for stroke prevention in a broad range of Chinese AF patients.

Even amongst low risk patients with AF, use of aspirin did not reduce thromboembolism, but had a tendency to more bleeding and intracranial bleeding [34].

Despite the (very) weak data for aspirin, as well as the poor efficacy and safety for aspirin in stroke prevention for AF, the use of aspirin is highly prevalent in many Asian countries (eg. China) [35] and its use continues to be recommended in some country-specific treatment guidelines, putting patients at risk of stroke and exposing them to aspirin-related bleeding.

### **Anticoagulation in Asian patients**

#### *Data on warfarin in Asians*

In the 4 recent Phase 3 trials comparing NOACs to warfarin, a consistent pattern is

evident. There were generally higher rates of stroke/systemic embolism (the primary efficacy endpoint), ischaemic stroke and haemorrhagic stroke on warfarin in Asians vs non-Asians, despite similar or lower CHADS<sub>2</sub> scores [Figure 1] [16-19]. All-cause mortality was higher in Asians on warfarin, compared to non-Asians in RE-LY, but not in the other 3 trials. Myocardial infarction events tended to be lower in Asian patients compared to non-Asians, in all the trials.

For safety endpoints, rates of major bleeding, intracranial bleeding and 'all bleeding' were also higher in Asians compared to non-Asians [Figure 2] [16-19]. In RE-LY, the risk of gastrointestinal bleeding was also higher in Asians, but lower in ENGAGE-AF.

The higher rates of serious bleeding may be related to the tendency to poorer TTRs in Asians [Figure 3], but other considerations, including the higher proportion of prior stroke/TIA amongst Asian subjects. [16-19][36] Poorer TTRs in Asians have been attributed to diet, herbal medicines, etc [37, 38]; however, the lack of structured anticoagulation services in many Asian countries may be an added logistic issue that precludes effective VKA management.

*Data on NOACs in Asians*

Forest plots showing relative risk reductions in Asians vs Non-Asians for the efficacy endpoints of stroke+systemic embolic events, ischemic stroke, hemorrhagic stroke, MI and all-cause death, are shown in Figure 4 [16-19]. Notwithstanding the limitations of indirect comparisons, given the smaller size cohorts of the Asians, a significant reduction in stroke/SE was seen for dabigatran 150mg [HR 0.45 (0.28-0.72)], with non-significant trends seen for lower stroke/SE with dabigatran 110mg, rivaroxaban, apixaban and edoxaban 60mg.

A similar pattern was seen for ischaemic stroke, with a significant reduction seen for dabigatran 150mg [HR 0.55 (0.32-0.950)], with a trend towards higher rates seen for edoxaban 30mg. For haemorrhagic stroke, all NOAC regimes had significantly lower hazard ratios, with a non-significant trend for rivaroxaban 20mg. For myocardial infarction, the non-significant trend seen for a numerical excess seen for dabigatran (both doses) and edoxaban 30mg amongst non-Asians, was reversed amongst Asians.

In ARISTOTLE, there was a non-significant trend towards more MIs with apixaban compared to warfarin [HR 1.17 (0.42-3.23)]. All-cause mortality was significantly lowered amongst Asian patients on edoxaban 60mg compared to warfarin [HR 0.63 (0.40-0.98)] with non-significant trends to lower mortality with dabigatran 150mg, rivaroxaban and edoxaban 30mg.

Corresponding absolute risk reductions for efficacy endpoints are shown in Figure 5 [16-19].

Similar forest plots for the safety endpoints of major bleeding, ICH, GI bleeding, and all bleeding are shown in Figure 6 [16-19]. Major bleeding was significantly lower amongst Asians on all the NOACs compared to warfarin, except for rivaroxaban 20mg. For ICH, all the NOACs had significantly lower rates compared to warfarin amongst Asians (and non-Asians). For gastrointestinal bleeding, the higher bleeding rates in non-Asians seen with dabigatran 150mg and edoxaban 60mg when compared to warfarin were reversed, showing a non-significant trend towards being lower in Asians. For the endpoint of 'all bleeding' in Asians this was significantly lowered with all NOACs, except for rivaroxaban, when compared to warfarin.

Corresponding absolute risk reductions for safety endpoints are shown in Figure 7 [16-19].

A summary table showing the efficacy and safety of NOACs in Asians (Table 3) clearly shows the main advantages of all the NOACs with lower haemorrhagic stroke and ICH,

compared to warfarin [16-19]. For major bleeding and 'all bleeding' this was significantly lower for all NOACs, with the exception of rivaroxaban.

The net clinical benefit balancing stroke reduction against bleeding is generally in favour of anticoagulation in patients with  $\geq 1$  stroke risk factors [39], with the greater benefit seen for those at highest risk of stroke and bleeding. In a modeling analysis, this was even more evident for the NOACs, compared to warfarin, in patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $\geq 1$  [40] and this also applies to Asian patients [35].

However, net clinical benefit can be defined in different ways. In RE-LY, the net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction including silent myocardial infarction, death, or major bleeding, and this was consistently in favor of both doses of dabigatran compared with warfarin, in both Asians and non-Asians. Only the dabigatran 150 mg dose in Asians was clearly superior versus warfarin (HR, 0.66; 0.52–0.83) [16].

Another consideration is the cost-effectiveness of these agents. The NOACs are new drugs and thus, expensive when simply comparing drug costs against the older drug, warfarin. The latter has additional costs in relation to INR monitoring, as well

as the various drug-related limitations (eg. diet, alcohol and drug restrictions) – in addition to the differences in efficacy and safety compared to NOACs. Various cost-effectiveness analyses have been published related to different healthcare systems. In the United Kingdom, for example, the NICE and SIGN (The Scottish Intercollegiate Guidelines Network) undertake cost-effectiveness analysis, and all 3 licensed NOACs (dabigatran, rivaroxaban, apixaban) have been shown to be cost-effective options instead of warfarin. Cost-effectiveness data from Asian countries are more limited, given the different healthcare systems. In Taiwan, one analysis for dabigatran clearly shows the cost-effectiveness of this NOAC [41].

### **A practical approach**

Rather than focus on targeting 'high risk' patients for OAC use, a clinical practice shift is needed, so that the initial step is identification of the 'truly low risk' patients with AF. These 'truly low risk' patients are those 'age <65 and lone AF (both male and female)', essentially a CHA<sub>2</sub>DS<sub>2</sub>-VASc score=0 (male) or 1 (female). Subsequently, OAC can be offered to all other patients with ≥1 stroke risk factors. Ultimately

effective stroke prevention requires OAC use, whether delivered as a NOAC or as well-controlled VKA (TTR>70%). Aspirin should not be used for stroke prevention in AF, given its inefficacy, poor safety and lack of cost effectiveness [31].

Practical aspects of managing individual NOACs have addressed in numerous reviews [42-44]. Guideline or prescribing label-adherent use of dabigatran has been shown to result in better efficacy and safety outcomes. Post-marketing 'real world' data for the NOACs have also confirmed the efficacy and safety of these agents [45, 46].

Should all newly diagnosed patients with AF be started on a NOAC? In some healthcare settings, a 'warfarin stress test' is mandated, to see if a satisfactory TTR can be achieved after 3-6 months. Given that TTRs tend to be poor during the inception phase of introducing warfarin, such an approach may put patients at increased risk of stroke (>70% increased) [47]. A simple score based on clinical factors (SAmE-TT<sub>2</sub>R<sub>2</sub>) (Sex, Age [<60 years], Medical history, Treatment [interacting drugs eg amiodarone], Tobacco use [doubled], and Race (non-Caucasian) [doubled]) has recently been proposed to help identify upfront those patients less likely to do well on VKA (SAmE-TT<sub>2</sub>R<sub>2</sub> score >2), where a NOAC or more intensive anticoagulation management can be applied [48]. The SAmE-TT<sub>2</sub>R<sub>2</sub> score has been shown to be

predictive of poor TTRs and labile INRs, and as a consequence, a resultant increase in risk of thromboembolism, death and bleeding [49-51]. The SAME-TT<sub>2</sub>R<sub>2</sub> score requires validation (or calibration) in Asian populations.

Irrespective of TTR, the benefits of NOACs on lowered haemorrhagic stroke and ICH compared to warfarin are maintained. However, the impact on stroke/SE and major bleeding may be less evident at the high TTRs. For example, in the case of either rivaroxaban or dabigatran, a reduction in one-year medical costs was no longer observed as warfarin's TTR increased above 65% and 70 %, respectively [52]. However, the use of apixaban was associated with a medical cost reduction across all warfarin TTR ranges evaluated (30–90%). Given that average TTRs in many Asian countries are poor, NOACs would seem the best option unless substantial improvements in the quality of anticoagulation control are achieved.

## Conclusions

Given the huge burden of AF and its complications related to stroke/SE in Asian countries, more attention to stroke prevention is clearly needed. Patients place



more emphasis on stroke prevention than physicians. In one recent study, patients were prepared to sustain 4 major bleeds, just to avoid one stroke which was viewed as a fate worse than death [53]. In contrast, physicians were more concerned with bleeding, at the cost of patients sustaining strokes [54]. Unless VKA management improves substantially, contemporary data from the warfarin arms of recent clinical trials shows how Asian patients do worse, with higher rates of thromboembolism and bleeding. By contrast, the preferred OAC treatment option in Asians with AF for stroke prevention would be a NOAC. A suggested flow chart for the management of non-valvular AF is illustrated in Figure 8.

A change in clinical approach, towards initially identifying 'low risk' patients using the CHA<sub>2</sub>DS<sub>2</sub>-VASc, then subsequently offering OAC to others with  $\geq 1$  stroke risk factors would have a major impact on reducing strokes and death on a population-wide basis [7, 55]. The HAS-BLED score can be used to flag up patients potentially at risk of bleeding, and to address the potentially correctable risk factors. Risk assessment is a continuous and dynamic process, and appropriate application of guidelines would result in better outcomes for our patients, reducing the major burden of AF-related stroke in Asia.

ACCEPTED MANUSCRIPT

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**Figure legends:**

**Figure 1.** Major cardiovascular events on warfarin in Asians vs non-Asians, from the randomised trials. A. Stroke and systemic embolization events; B. Ischaemic stroke; C. Haemorrhagic stroke; D. Myocardial infarction; E. All-cause death.

**Figure 2.** Bleeding events on warfarin in Asians vs non-Asians, from the randomised trials. A. Major bleeding; B. Intra-cranial haemorrhage; C. Gastrointestinal bleeding; D. All (major plus minor) bleeding episodes.

**Figure 3.** International normalized ratios (INRs) in the randomised trials. Asians in RE-LY included patients from China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, and India[16]. Asians in ROCKET included patients from China, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, and Thailand[36]. Asians in ARISTOTLE included patients from China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, and Malaysia[18]. East Asians in ENGAGE included patients from China, Japan, South Korea, and Taiwan[19].

**Figure 4.** Forest plots for efficacy endpoints with NOACs vs warfarin in Asians vs non-Asians, from the randomised trials. A. Stroke and systemic embolization events; B. Ischaemic stroke; C. Haemorrhagic stroke; D. Myocardial infarction; E. All-cause death. Lines of confidence interval and points of estimation were shown in red color for Asians and black color for non-Asians. NOACs = non-vitamin K antagonist oral anticoagulants

**Figure 5.** Absolute risk reductions in efficacy endpoints with NOACs vs warfarin in Asians vs non-Asians, from the randomised trials. In general, the absolute risk reductions were numerically greater in Asians than in non-Asians. A. Stroke and systemic embolization events; B. Ischaemic stroke; C. Haemorrhagic stroke; D. Myocardial infarction; E. All-cause death.

**Figure 6.** Forest plots for safety endpoints with NOACs vs warfarin in Asians vs non-Asians, from the randomised trials. A. Major bleeding; B. Intra-cranial haemorrhage; C. Gastrointestinal bleeding; D. All (major plus minor) bleeding episodes. Lines of confidence interval and points of estimation were shown in red color for Asians and black color for non-Asians. NOACs = non-vitamin K antagonist oral anticoagulants

**Figure 7.** Absolute risk reductions in safety endpoints with NOACs vs warfarin in Asians vs non-Asians, from the randomised trials. In general, the absolute risk reductions were numerically greater in Asians than in non-Asians. A. Major bleeding; B. Intra-cranial haemorrhage; C. Gastrointestinal bleeding; D. All (major plus minor) bleeding episodes.

**Figure 8.** Flow chart for the management of non-valvular AF in Asians. AF = atrial fibrillation; CHA2DS2-VASc = Congestive heart failure, Hypertension, Age  $\geq 75$  [doubled], Diabetes, Stroke [doubled]-Vascular disease, Age 65–74, Sex category [female]; NOACs = non-vitamin K antagonist oral anticoagulants



Table 1. Co-morbidities of AF in Asians vs non-Asians in survey and cohorts

	Asians					Non-Asians				
	J-Rhythm[9]	HK[3]	RECORDAF AP[10]	REALISEAF Asia[11]	RELY AF SouthEast Asia[12]	ORBIT AF[13]	Euro Heart Survey[14]	RECORDAF[15]	REALISEAF Europe[11]	RELY AF West Europe[12]
CHF (%)	34.4	22.8	25	35.7	26.3	32	33	26	33.2	21.2
Hypertension (%)	71.1	54.7	58	67.5	64.1	83	63	68	78.1	59.9
Age (mean) (%)	69.7	76.9	64	66.4	69.5	75	66	66	68.1	69.4
Diabetes (%)	22.1	22.0	18	24.9	29.2	29	18	16	20.2	17.1
Stroke/TIA (%)	17.3	23.1	13	21.9	22.1	16	9	10	13.5	12.0
CHD (%)	11.6	18.2	19	32.8	10.9*	32	32	18	36.4	18.2*
Female (%)	31.1	52.1	40	45.9	44.6	42	43	43	40.4	38.8

CHD: coronary heart disease; CHF: congestive heart failure; TIA: transient ischemic attack

\*: prior myocardial infarction

Table 2. Co-morbidities of AF in Asians vs non-Asians in clinical trials

	Heart failure (%)	Hypertension (%)	Age≥75 (%)	Diabetes (%)	Stroke/TIA (%)	Mean CHADS <sub>2</sub> score
RE-LY[16]						
Asians (n=2,782)*	36.3	71.2	27.4	25.1	24.2	2.2
Non-Asians (n=15,331)	31.2	80.2	42.2	23.0	10.4	2.1
ROCKET[17]			(mean age)			
East Asians (n=932)†	38.6	79.9	69.7	36.9	65.0	3.2
Non-East Asians (n=13,322)	64.1	91.3	71.3	40.1	54.0	3.5
ARISTOTLE[18]						
Asians (n=1,993)‡	26.2	82.3	24.4	25.2	28.8	2.1
Non-Asians (n=16,202)	36.6	88.1	32.0	25.0	18.3	2.1
ENGAGE[19]						
East Asians (n=1,943)§	47.3	82.1	37.5	35.0	42.4	2.9
Non-East Asians (n=19,162)	58.5	94.8	40.4	36.2	26.9	2.8

TIA: transient ischemic attack

\*: China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India

†: China, South Korea, Taiwan, Hong Kong

‡: China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia

§: China, Japan, South Korea, Taiwan

Table 3. Efficacy and safety endpoints of different NOACs in Asians

	Stroke/SEE	Ischemic stroke	Hemorrhagic stroke	Myocardial infarction	All-cause death	Major bleeding	Intra-cranial hemorrhage	GI bleeding	All bleeding
Dabigatran* 150 mg	v	v	v			v	v		v
Dabigatran* 110 mg			v			v	v		v
Rivaroxaban†							v		
Apixaban‡			v			v	v		v
Edoxaban§ 60 mg			v		v	v	v		v

Edoxaban§			v			v	v		v
30 mg									

GI: gastrointestinal; SEE: systemic embolization events

\*: China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.

†: China, South Korea, Taiwan, Hong Kong

‡: China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia

§: China, Japan, South Korea, Taiwan

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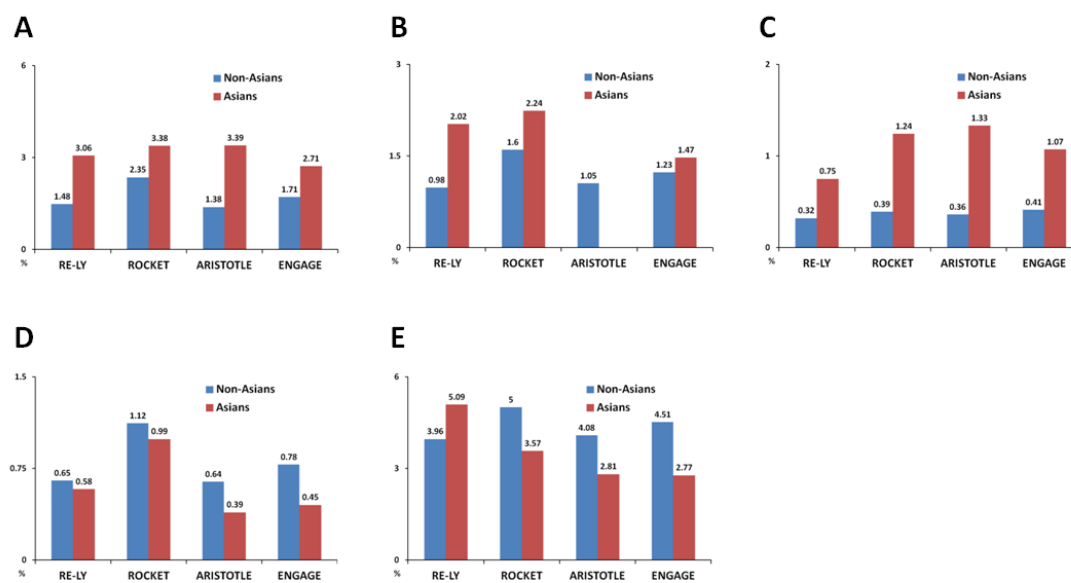


Fig. 1

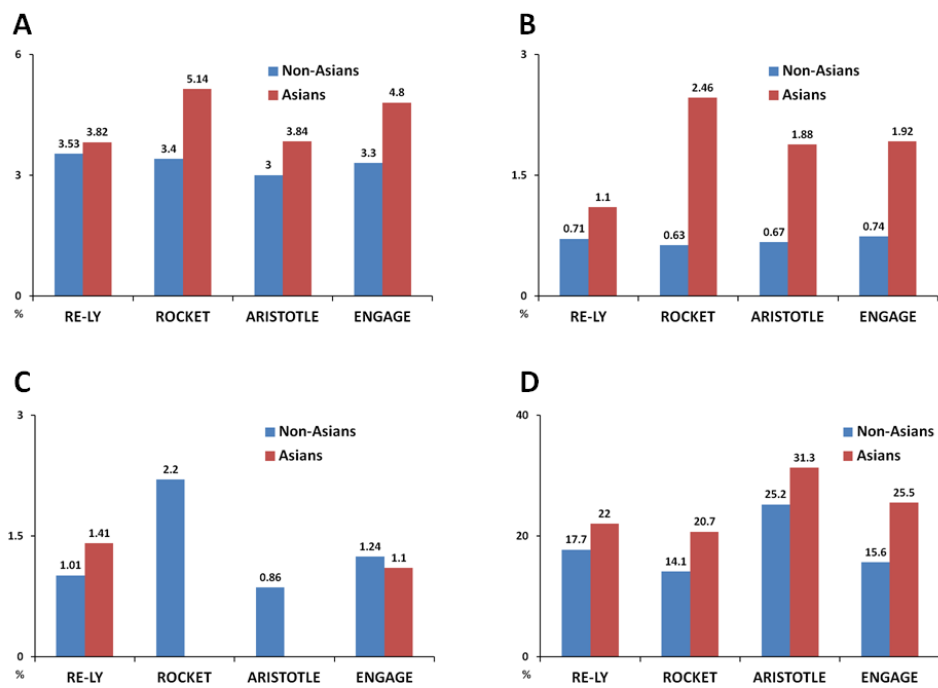


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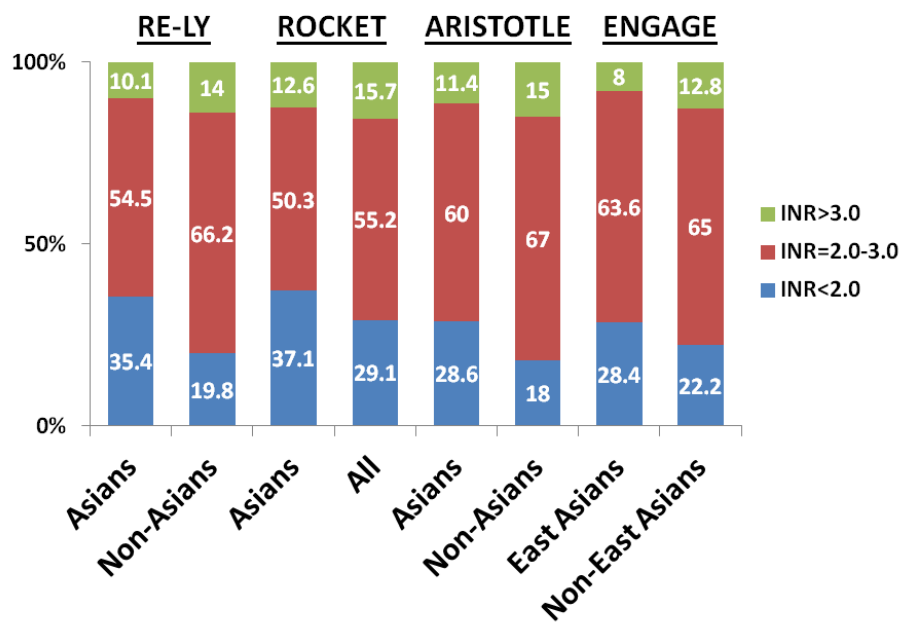


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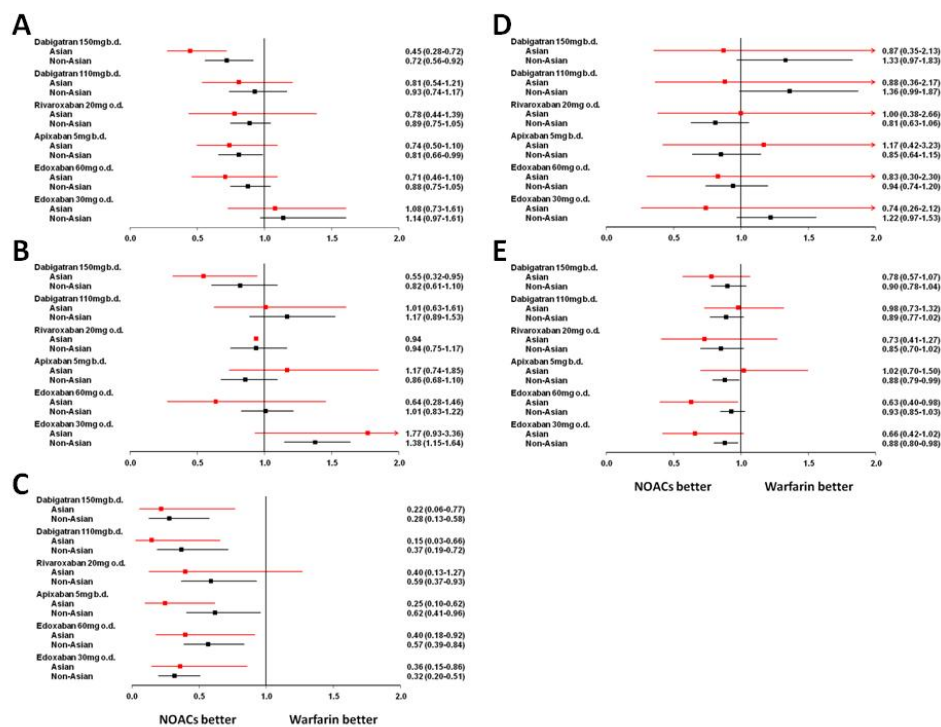


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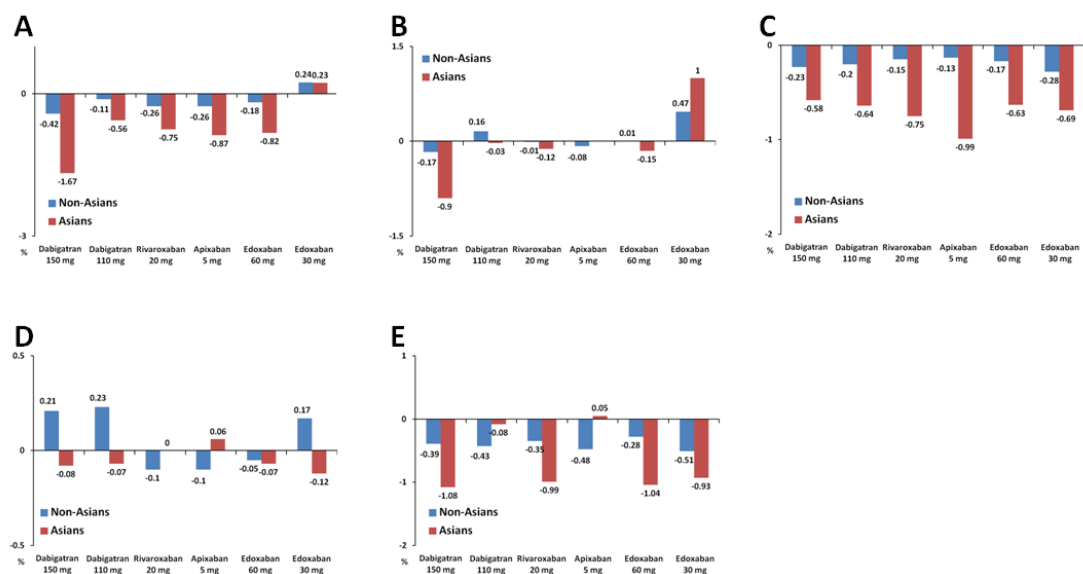


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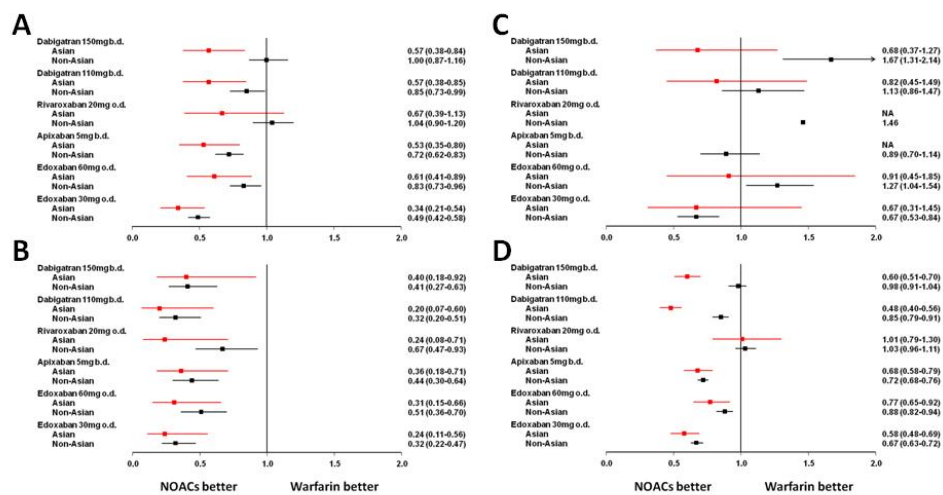


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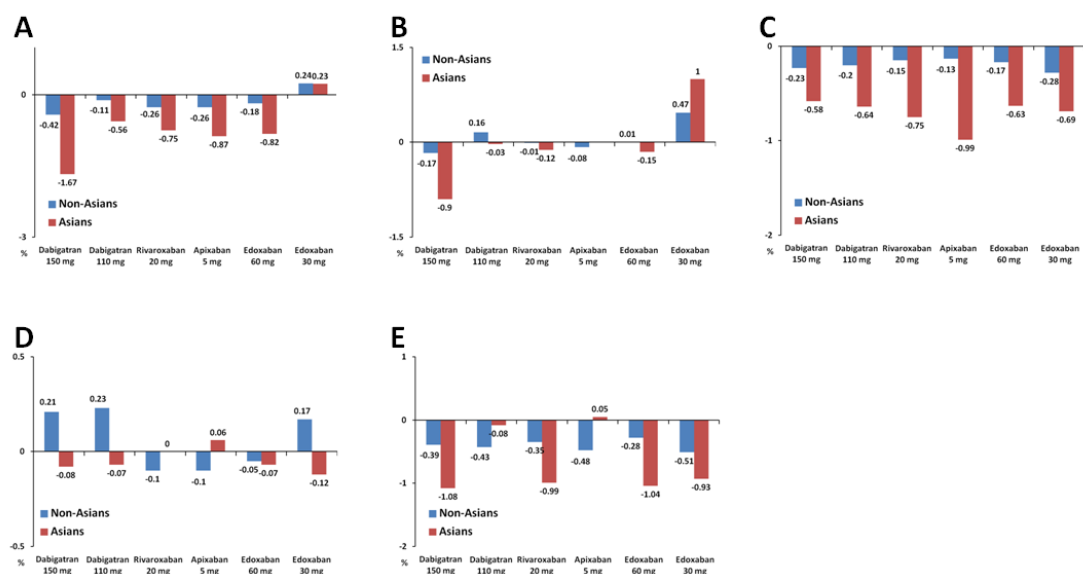


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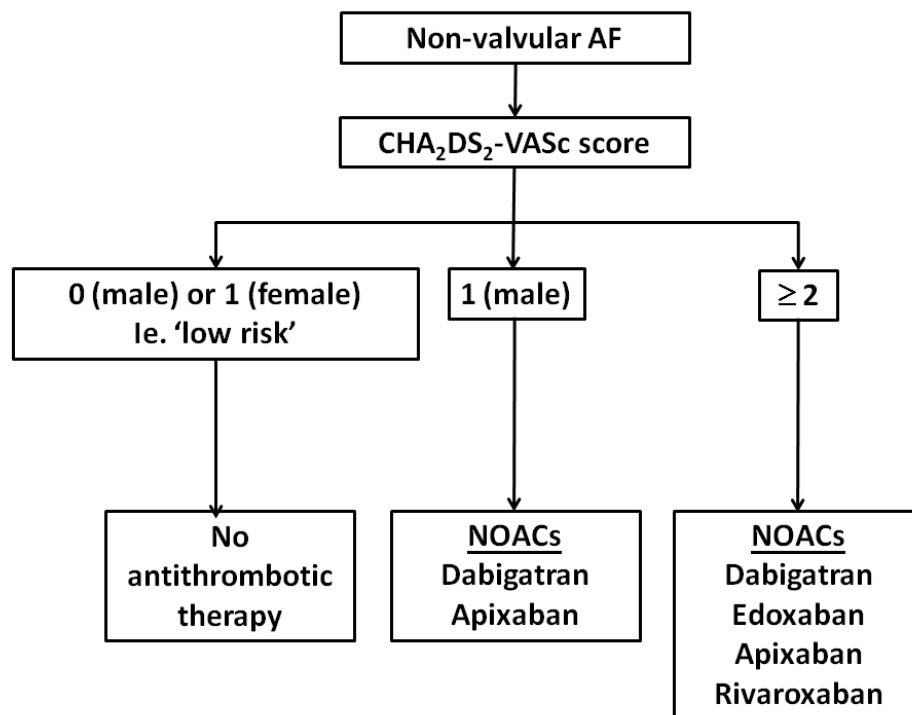


Fig. 8

### Highlights

- Data for Asians vs non-Asians were systemically reviewed in 4 megatrials of NOACs.
- Warfarin induced more major bleeding and intracranial hemorrhage in Asians.
- Bleeding events were generally lower for NOACs than Warfarin in Asians.
- NOACs were superior or non-inferior to warfarin in stroke prevention in Asians.
- NOACs should be preferentially indicated for stroke prevention in Asians with AF.